Remarks

Claims 1 and 2 are pending.

Rejection Under 35 U.S.C. § 103

Claims 1 and 2 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Georgadze et al. (*Vestn Khir Im I I Grek* 142(3):20-24. 1989), in view of Malchesky et al. (US 4,350,156) and further in view of Hunter (US 5,152,979). The Office action alleges that Georgadze et al. teach that "plasmapheresis may be used for the treatment of ischemia in the lower extremities of diabetics;" that Malchesky et al. teach the "plasmafiltration of blood for the removal of high molecular weight proteins;" and that Hunter "generally teaches that ischemia causes increased viscosity of blood and recognizes that increased whole blood viscosity is capable of causing serious circulatory disturbances."

Based on this understanding, the Office Action posits that it would have been obvious to modify the method of Georgadze et al. to specifically remove high molecular weight protein, such as lipoprotein cholesterol, as allegedly taught by Malchesky et al. since both allegedly teach removal of protein from the blood to achieve a therapeutic result, such as returning blood to its normal viscosity, and since both of these procedures of "plasmapheresis of blood" and "plasmafiltration of blood" are analogous fields of endeavor. The Office Action further posits that Hunter allegedly teaches that ischemia causes impaired circulation because of blood hyperviscosity.

Applicants respectfully traverse this rejection on the basis that the Office Action has not established *prima facie* obviousness, and that even if such a standard has been met, there are secondary considerations that rebut a finding of obviousness.

Notably, Applicants provided extrinsic evidence in the response filed December 12, 2005 that to date has not even been acknowledged, despite Applicant's reference thereto in the Response filed July 6, 2006 and the specific request that the evidence be given its due specific consideration in the Response filed January 11, 2007. The evidence included a letter from Dr. Schmid-Schönbein, who is the former Director of the Department of Physiology, University of Aachen, and an internationally recognized expert in rheology. The letter explained the concept of hemorheology and noted the failure of the prior art to suggest its application for the treatment of diseases such as diabetic ischemia of a foot. The letter of Dr. Schmid-Schönbein also acknowledged the significant contribution of the present invention to the art of treating diabetes. Applicant also included evidence that the claimed method has been adopted and accepted by the industry. *See* Richter et al. (Transfus Apher Sd. 2002 Feb;26(1): 15-27) and Klingel et al. (Ther Apher Dial. 2003 Aug; 7(4):444-55). For the Office not to consider all rebuttal arguments and evidence presented by applicants is legal error. Applicants therefore respectfully request that the Office give due consideration to the evidence previously submitted and to the additional evidence provided herein.

A. Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *See In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967); *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the

invention would have a reasonable likelihood of success. *See In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The Supreme Court recently reaffirmed the factors for determining of obvious under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007). The four factual inquiries under *Graham* are:

a) the scope and contents of the prior art;
b) the differences between the prior art and the claims in issue;
c) the level of ordinary skill in the pertinent art; and
d) evidence of secondary consideration.

Graham v. John Deere (*Graham*), 383 U.S. 1, 17-18, 149 USPQ 459, 467 (1966). In affirming these factors, however, the Court further recognized that the requirement for a teaching, suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, still provides a helpful insight for determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). In addition, the Court maintained that any analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that it is "important to identify reasons that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed, because "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR,* 127 S.Ct. at 1741. Further, the Court, citing *Graham*, indicated that "a factfinder [*sic*] should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR,* 127 S.Ct. at 1742.

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, a showing of *prima facie* obviousness requires that one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 127 S.Ct. at 1739.

If a *prima facie* case of obviousness is established, Applicant can provide evidence to rebut the *prima facie* case. It is legal error for the Office not to consider all rebuttal arguments and evidence presented by applicants. *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687 (error not to consider evidence presented in the specification); *In re Beattie*, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1042-43 (Fed. Cir. 1992) (Office personnel should consider declarations from those skilled in the art praising the claimed invention and opining that the art teaches away from the invention.); *Piasecki*, 745 F.2d at 1472, 223 USPQ at 788 ("[Rebuttal evidence] may relate to any of the Graham factors including the so-called secondary considerations.").

Rebuttal evidence includes evidence of secondary considerations, such as unexpected results, long felt but unmet need in the art, commercial success, and recognition in the industry. *Graham v. John Deere Co.*, 383 U.S. at 17, 148 USPQ at 467. Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F.2d at 692-93, 16 USPQ2d at 1901. Rebuttal evidence may include evidence that the claimed invention was copied by others. See, e.g., *In re GPAC*, 57 F.3d 1573, 1580, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); *Hybritech*

Inc. v. Monoclonal Antibodies, 802 F.2d 1367, 1380, 231 USPQ 81, 90 (Fed. Cir. 1986). It may also include evidence of the state of the art, the level of skill in the art, and the beliefs of those skilled in the art. See, e.g., *In re Oelrich*, 579 F.2d 86, 91-92, 198 USPQ 210, 214 (CCPA 1978).

B. Analysis

Georgadze et al. teach the use of plasma exchange to extract bacterial toxins, circulating immunocomplexes (CIC), and killer cells associated with diabetic angiopathies. This is a non-specific removal of the plasma, which must be replaced with a plasma substitution fluid. There is no indication by Georgadze et al. that removal of only high molecular weight proteins would be sufficient to achieve the desired result. Further, there was no teaching that modification of the blood viscosity would have a therapeutic benefit to diabetic ischemia. Malchesky et al. does not correct this deficiency.

Malchesky et al. teaches generally the removal of macromolecules at predetermined sizes from blood for the purpose of removing abnormal metabolites or toxins. They recognize that plasmapheresis methods are being used for a host of diseases, including diabetes, but only apply their method to diseases with known correlations between the disease and increased levels of specific plasma factors (column 2, lines 22-27). However, there is no indication in Malchesky et al. or any of the cited references that diabetic ischemia of the foot can be correlated with any factors other than those specifically disclosed or with the presence of high molecular weight proteins in general. While it is true that Malchesky et al. reference hyperviscosity as a factor in hypertriglyceridemia (see Table 2), they do not suggest that hypertriglyceridemia is correlated with diabetic ischemia of the foot, and they do not suggest removal of high molecular weight

proteins. Instead, consistent with their other teaching, Malchesky et al. treat triglycerides as a specific plasma factor that would need to be removed to treat triglyceridemia.

Thus, there is no teaching, suggestion, or motivation to combine the teachings of Georgadze et al. and Malchesky et al. to arrive at the claimed method of removing high molecular weight proteins to treat diabetic ischemia. In order to attempt to correct this deficiency, the Office Action cites Hunter, who recognized that circulatory disturbances can be produced through blocking of the capillaries by clumped erythrocyes and phagocytes, increased blood and plasma viscosity, and slowing of circulatory circulation (paragraph bridging columns 3 and 4). However, viscosity was only one factor mentioned and there was no indication that it could be a potential therapeutic target. Instead, Hunter teaches administering a surface active polymer to reduce the friction from nonspecific physicochemical adhesion to treat ischemia resulting from microvascular compromise caused by abnormal cells in the blood stream as a result of malaria and leukemia (abstract). Hunter does not teach treating diabetic ischemia, nor does he suggest that it is caused by a problem with blood viscosity. He does not teach removal of high molecular weight proteins. And, he does not teach alteration of blood viscosity. As such, the skilled artisan would not have been motivated to combine Georgadze et al., Malchesky et al., and Hunter. And, even if so motivated, the combination would not produce the claimed method. That is, the skilled artisan would not have been led to remove high molecular weight proteins based on this combination. Recognition that viscosity is involved in circulatory disturbances would not have reasonably led the skilled artisan to conclude that viscosity could be manipulated or that removal of the high molecular weight proteins would achieve this result. The Examiner is therefore using impermissible hindsight based on evidence provided in the instant disclosure that

removal of high molecular weight proteins from the blood is sufficient to treat diabetic ischemia of the foot.

Moreover, even if the skilled artisan had been motivated to combine the teachings of Georgadze et al., Malchesky et al. and Hunter in the manner suggested by the Office Action, there would not have been a reasonable expectation of success that removal of high molecular weight protein from the blood would have been effective at treating diabetic ischemia. Neither Georgadze et al. or Hunter taught the removal of high molecular weight proteins or suggested any benefit for doing so. And, whereas Malchesky et al. taught the removal of specific plasma macromolecules that were correlated to the specific diseases, none of Georgadze et al., Malchesky et al., or Hunter sufficiently correlated high molecular weight proteins or plasma viscosity to diabetic ischemia of the foot in a manner sufficient to yield a predictable result. *See KSR* 127 S.Ct. at 1739. In contrast, it was in fact not reasonably predicted prior to the instant application that plasmafiltration of high molecular weight proteins would be sufficient to treat diabetic ischemia of the foot.

Applicants provide evidence herewith in the form of a Declaration under 37 C.F.R. § 1.132 by inventor Dr. Helmut Borberg (attached as **Exhibit A**) declaring *inter alia* that:

a) at the time the application was filed, the skilled artisan reading Georgadze et al., Malchesky et al. and Hunter would not have been motivated to remove high molecular weight proteins from the blood to treat diabetic ischemia; and
b) even if attempted, there would have been no reasonable expectation of success that removal of high molecular weight protein from the blood would have been effective at treating diabetic ischemia.

Additional evidence of non-obviousness is found in the letter from Dr. Schmid-Schönbein provided in the response filed December 12, 2005, wherein he stated "the relevance of differential separation techniques for extracorporeal hemorheotherapy [had] neither been taken into consideration nor investigated before the [instant] patent application ..."

Applicants therefore respectfully submit that *prima facie* obviousness has not been established and request the withdrawal of the rejection.

C. Rebuttal Evidence

Furthermore, even if *arguendo* a showing of *prima facie* obviousness could be established by the teachings of Georgadze et al., Malchesky et al. and Hunter, Applicants submit rebuttal evidence that the scientific community has recognized the long felt but unmet need in the art satisfied by the invention, the commercial/ clinical success of the claimed approach, the recognition of the invention by the field, and evidence that the claimed invention was copied/ adopted by others in the field since the publication by the inventor. For example, Dr. Borberg stated in the Declaration under 37 C.F.R. § 1.132 that "the scientific community has recognized the success of the claimed approach since the publication ..."

Likewise, in the letter provided in the response filed December 12, 2005, Dr. Schmid-Schönbein recognized the significant contribution of the claimed method to the art of treating diabetes, stating "that it has to be considered an innovative breakthrough for both clinical hemorheology and diabetes treatment." This is evidence of clinical success and recognition of the invention by the field since the publication by the inventor.

Also submitted is a declaration by Dr. Paul Hoecker (attached as **Exhibit B**), who is Professor of Medicine Primarius and Director emeritus in the Department of Transfusion

Medicine and Immunohaematology at the University of Vienna. His declaration evidences the invention's satisfaction of a long felt but unmet need in the art as well as its commercial (clinical) success. Dr. Hoecker states in his declaration that the claimed therapeutic approach "is of original unique nature, heavily cited and continuously internationally expanding not only in Germany but also in Austria, Canada, France, Italy, Japan, United States of America, Russia and others" and "unique in a way that is based on haemorheological investigations not taken into consideration from other investigators." Moreover, Dr. Hoecker attests that the claimed method is "well suited to cure patients without treatment alternative." In addition to showing commercial/ clinical success of the claimed approach, this is further evidence that the scientific community has recognized the long felt but unmet need in the art satisfied by the claimed method.

Moreover, industrial recognition is evidenced in Richter et al. (Transfus Apher Sd. 2002 Feb;26(1): 15-27, **of record**), who demonstrate that elimination of fibrinogen from plasma decreased whole blood viscosity, which resulted in accelerated wound healing in patients with foot ulcers resulting from diabetes (abstract). In addition to showing adoption and clinical success of the claimed approach, the publication of this article in a peer review journal shows that the effect disclosed was not obvious (if it was obvious, it would not have been worthy of publication).

Likewise, Klingel et al. (Ther Apher Dial. 2003 Aug; 7(4):444-55, **of record**) demonstrated that removal of high molecular weight proteins, including LDL cholesterol, fibrinogen, α2-macroglobulin, von Willdebrand factor (vWF) and fibronectin), which results in lower blood viscosity, can preserve a functional lower extremity, delay amputation, or reduce the

extent of amputation in diabetic ischemia of the foot (abstract). This is likewise evidence that the claimed method has been adopted by the field and demonstrated significant clinical success.

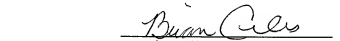
Applicants provide additional publications herewith to demonstrate industrial recognition and copying of the claimed method. Klingel R et al. 2000 (Therapeutic Apheresis 2000 4(5):348-357, attached as **Exhibit C**) is a review that explains the principles of extracorporeal haemorheotherapy due to the elimination of high molecular weight proteins leading to an improvement of the blood rheology and thus improvement to the microcirculation. Notably, the inventor is given due credit for the discovery that rheopheresis results in an improvement of blood and plasma viscosity (page 348, second paragraph). Likewise, Klingel R et al. 2003 (Therapeutic Apheresis 2003 7(4): 444-455, attached as **Exhibit D**) and Klingel R et al. 2005 (Therapeutic Apheresis and Dialysis 2005 9(6):473-481, attached as **Exhibit E**) described the efficacy of treating patients suffering from diabetic foot syndrome using the claimed method. These references represent additional evidence of clinical success and adoption in the field.

Applicants therefore submit that the above evidence of secondary consideration is sufficient to rebut a conclusion of obviousness. Applicants therefore respectfully request the withdrawal of the present rejection and allowance of claims 1 and 2.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment authorizing payment in the amount of $525.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(3) for a Three Month Extension of Time, a Request for Extension of Time, and Exhibits (A-E) are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,
NEEDLE & ROSENBERG, P.C.



P. Brian Giles, Ph.D.
Registration No. 57,896

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8			
I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.			
Name of Person Mailing (Print/Type)	P. Brian Giles, Ph.D.		
Signature		Date	4-22-2008